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(71) Applicant *(for all designated States except US)*: BAYER AKTIENGESELLSCHAFT [DE/DE]; D–51368 Leverkusen (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: STURTON, Graham [GB/GB]; 184 Windsor Road, Maidenhead, Berkshire, SL6 2DW (GB). FITZGERALD, Mary, F. [GB/GB]; 2 Paternoster Court, Cassington Road, Yarnton, Oxford OXS 1QB (GB). BRIGGS, Barbara, A. [GB/GB]; 24 Latchmere Road, Kingston, Surrey KT2 5TN (GB). CONCEPCION, Arnel [PH/JP]; 3–6–207 Shibatsuji.cho, Nara City, Nara (JP). BULLOCK, William [US/US]; 60 Hermann Lane, Easton, CT 06612 (US). BRÄUNLICH, Gabriele [DE/DE]; Claudiusweg 9, D–42115 Wuppertal (DE). ES–SAYED, Mazen [DE/DE]; Ricarda–Huch–Str. 36, D–40764 Langenfeld (DE). FISCHER, Rüdiger [DE/DE]; Christian–Gau–Str. 33, D–50933 Köln (DE). FUGMANN, Burkhard [DE/DE]; Dr.–Kessel–Str. 3, D–40878 Ratingen (DE). HENNING, Rolf [DE/DE]; Am Jagdhaus 115, D–42113 Wuppertal (DE). SCHNEIDER, Stephan [DE/DE]; Am Ringofen 46, D–42327 Wuppertal (DE). SPERZEL, Michael [DE/DE]; Normannenstr. 31, D–42275 Wuppertal (DE). SCHLEMMER, Karl–Heinz [DE/DE]; Wildsteig 22a, D–42113 Wuppertal (DE).

(74) Common Representative: BAYER AKTIENGESELLSCHAFT; D–51368 Leverkusen (DE).

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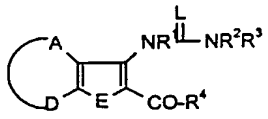

(I)

(57) Abstract

Cycloalkyl substituted 3–urea–benzofurane– and –pyridofurane–derivatives of general formula (I) for the treatment of inflammatory processes.

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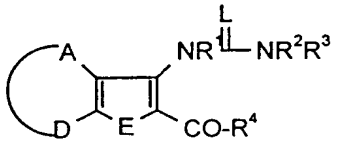
Cycloalkyl substituted 3-Urea-benzofurane- and -pyridofurane-derivatives

The invention relates to Cycloalkyl substituted 3-urea-benzofurane- and -pyridofurane-derivatives, processes for their preparation and their use in medicaments.

It is known that the NADPH oxidase of phagocytes is the physiological source to the superoxide radical anion and reactive oxygen species derived therefrom which are important in the defence against pathogens. Moreover, both inflammatory (e.g. TNFα, IL-1 or IL-6) and anti-inflammatory cytokines (e.g. IL-10) play a pivotal role in host defence mechanisms. Uncontrolled production of inflammatory mediators can lead to acute and chronic inflammation, tissue damage, multi-organ failures and to death. It is additionally known that elevation of phagocyte cyclic AMP leads to inhibition of oxygen radical production and that this cell function is more sensitive than others such as aggregation or enzyme release.

Benzofuran- and benzothiophene derivatives having phosphodiesterase (PDE IV)-inhibiting action are described in the publication EP 731 099. In order to provide alternative compounds with similar or improved PDE IV-inhibiting action, the present invention relates to Cycloalkyl substituted 3-urea-benzofurane- and -pyridofurane-derivatives of the general formula (I)



(I)

in which

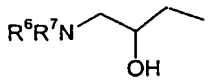
A and D including the double bond connecting them together form a phenyl-, pyridyl-, pyrimidyl, pyridazinyl- or thienyl-ring, which are substituted by a group of a formula -OR^5

wherein

R^5 denotes straight-chain or branched alkyl having up to 10 carbon atoms, which is substituted difold to fivefold by hydroxyl or difold to fivefold by straight-chain oder branched alkoxy having up to 6 carbon atoms and wherein alkyl is optionally substituted by straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms, halogen, carboxyl or by phenyl, which is optionally substituted by nitro or halogen,

or

denotes a group of a formula



or $-SO_2-G$,

in which

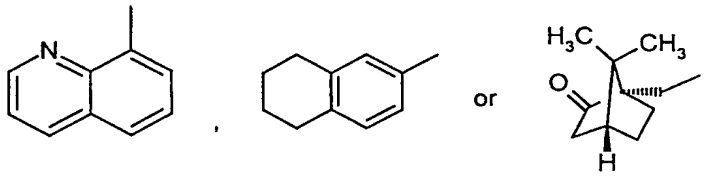
R^6 and R^7 denote hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by aryl having 6 to 10 carbon atoms or by a 5 to 7 membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused and which is optionally, including the nitrogenfunction, monosubstituted to disubstituted by identical or different substituents from the series comprising halogen, cyano or by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

or

R^6 and R^7 together with the nitrogen atom form a 5- to 6-membered, aromatic, saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused and which is optionally, including the nitrogenfunction, monosubstituted to disubstituted by identical or different substituents from the series comprising halogen, cyano or by straight-chain or branched alkyl or alkoxycarbonyl each having up to 6 carbon atoms,

and

G denotes a residue of a formula



or aryl having 6 to 10 carbon atoms or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused, wherein all abovementioned residues and ring systems are optionally monosubstituted to trisubstituted by halogen, carboxyl, straight-chain or branched alkyl or alkoxy-carbonyl each having up to 6 carbon atoms, pyridyl and/or by a residue of a formula $-NR^8-M-R^9$, $-NR^{10}-CO-NR^{11}R^{12}$, $-NR^{13}-SO_2-NR^{14}R^{15}$, $-SO_2-R^{16}$ or $-(SO_2)_n-NR^{17}R^{18}$,

wherein

a denotes a number 0 or 1,

M denotes a residue of formula SO_2 or CO

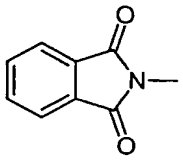
R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} and R^{18} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

R^9 denotes straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

R^{16} denotes benzyl, phenyl or methyl,

or

G denotes straight-chain or branched alkyl or alkenylen having up to 8 carbon atoms, which optionally are monosubstituted to trisubstituted by halogen, aryl having up 6 to 10 carbon atoms or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused or by a residue of a formula $-NR^{19}R^{20}$ or



wherein

R^{19} and R^{20} have the abovementioned meaning of R^{11} and R^{12} and are identical or different to the latter,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms, an amino protecting group or a group of the formula $-CO-R^{21}$

in which

R^{21} denotes straight chain or branched alkoxy having up to 4 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cycloalkyl having up to 6 carbon atoms, straight chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 8 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a 5- to 7-membered saturated heterocycle optionally having a further O atom,

R^4 represents cycloalkyl having up 3 to 8 carbon atoms which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, halogen, nitro, 1H-tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms or by a group of formula $-NR^{22}R^{23}$, $-SR^{24}$, $-(NH)_b-SO_2R^{25}$ or $-O-SO_2R^{26}$,

in which

R^{22} and R^{23} are identical or different and denote hydrogen or a straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^{22} denotes hydrogen

and

R^{23} denotes straight-chain or branched acyl having up to 6 carbon atoms

R^{24} denotes straight-chain or branched alkyl having up to 4 carbon atoms,

b denotes a number 0 or 1,

R^{25} and R^{26} are identical or different and represent straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, which are optionally substituted by trifluoromethyl, halogen or straight-chain or branched alkyl having up to 4 carbon atoms,

L represents an oxygen or sulfur atom

and salts thereof.

The cyclcoalkyl substituted 3-Urea-benzofurane- and -pyridofurane-derivatives according to the invention can also be present in the form of their salts and pyridinium oxide. In general, salts with organic or inorganic bases or acids may be mentioned here.

Physiologically acceptable salts are preferred in the context of the present invention. Physiologically acceptable salts of the cycloalkyl substituted 3-Urea-benzofurane and

-pyridofurane-derivatives can be metal or ammonium salts of the substances according to the invention, which contain a free carboxylic group. Those which are particularly preferred are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

Physiologically acceptable salts can also be salts of the compounds according to the invention with inorganic or organic acids. Preferred salts here are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid. Preferred pyridinium salts are salts in combination with halogen.

The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemate forms, as well as the diastereomer mixtures and individual diastereomers. The racemate forms, like the diastereomers, can be separated into the stereoisomerically uniform constituents in a known manner.

Heterocycle in general represents a 5- to 7-membered, aromatic, saturated or unsaturated, preferably 5- to 6- membered, aromatic, saturated or unsaturated ring which can contain up to 3 oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further aromatic ring can be fused.

The following are mentioned as preferred: thienyl, furyl, pyrrolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxazolyl, cinnolyl, thiazolyl, dihydrothiazolyl, benzothiaazolyl, isothiazolyl, benzisothiazolyl, oxazolyl.

benzoxazolyl, isoxazolyl, imidazolyl, benzimidazolyl, indolyl, morpholinyl, pyrrolidinyl, piperidyl, piperazinyl, oxazolinyl or triazolyl.

Preferred compounds of the general formula (I) are those

in which

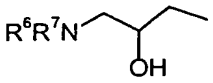
A and D, including the double bond connecting them form together a phenyl-, pyridyl- or pyridazinyl-ring, which are substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is substituted difold to fourfold by hydroxyl, and wherein alkyl is optionally substituted by straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms, fluorine, chlorine or by phenyl, which is optionally substituted by nitro, fluorine or chlorine,

or

denotes a group of a formula

 or $-SO_2-G$,

in which

R^6 and R^7 represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl, pyridyl, imidazolyl, pyrryl, morpholinyl, piperidinyl, piperazinyl or pyrrolidinyl, wherein the ring systems are

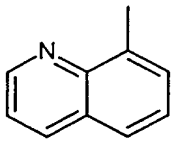
optionally, including the nitrogen function, monosubstituted by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

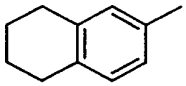
or

R^6 and R^7 together with the nitrogen atom form a pyrazolyl-, triazolyl-, tetrazolyl-, imidazolyl-, pyrryl-, morpholinyl-, piperidinyl-, pyrrolidinyl- or piperazinylring, wherein the ringsystems are optionally, including the nitrogen function, are monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, cyano or by a straight-chain or branched alkyl having up to 6 carbon atoms,

and

G represents a residue of a formula

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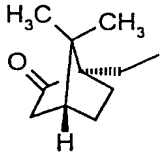


or phenyl, pyridyl, pyrimidyl, thienyl, furyl, pyrazolyl, isoxazolyl, thiazolyl, imidazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrrolidinyl or piperazinyl, wherein all abovementioned residues and ring systems are optionally monosubstituted to trisubstituted by halogen, carboxyl, straight-chain or branched alkyl or alkoxycarbonyl each having up to 4 carbon atoms, pyridyl and/or by a

residue of a formula $-NR^8-M-R^9$, $-NR^{10}-CO-NR^{11}R^{12}$, $-NR^{13}-SO_2-NR^{14}R^{15}$, $-SO_2-R^{16}$ or $-(SO_2)_a-NR^{17}R^{18}$,

wherein

a denotes a number 0 or 1,

M denotes a residue of formula SO_2 or CO

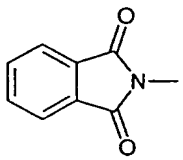
R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} and R^{18} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

R^9 denotes straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

R^{16} denotes benzyl, phenyl or methyl,

or

G represents straight-chain or branched alkyl or alkenylen having up to 6 carbon atoms, which are optionally monosubstituted to trisubstituted by halogen, phenyl, pyridyl, pyrimidyl, thienyl, furyl, imidazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl or by a residue of a formula $-NR^{19}R^{20}$ or



wherein

R^{19} and R^{20} have the abovementioned meaning of R^{11} and R^{12} and are identical or different to the latter,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms or a group of the formula -CO-R^{21}

in which

R^{21} denotes straight chain or branched alkoxy having up to 4 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 4 carbon atoms, or

or

R^2 and R^3 together with the nitrogen atom form a pyrrolidinyl-, piperidinyl- or morpholinyl-ring,

and

R^4 represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, fluorine, chlorine, bromine, nitro, tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having up to 4 carbon atoms, or by straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by

carboxyl or straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms

L represents an oxygen or sulfur atom,

and salts thereof.

Particularly preferred compounds of the general formula (I) are those

in which

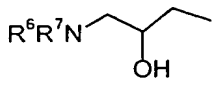
A and D, including the double bond connecting them form together a phenyl- or pyridyl-ring, which are substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is substituted difold to fourfold by hydroxyl, and wherein alkyl is optionally substituted by methoxycarbonyl, fluorine or by phenyl, which is optionally substituted by nitro or fluorine,

or

denotes a group of a formula



or $-SO_2-G$,

in which

R^6 and R^7 denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl, pyridyl, imidazolyl, pyrryl, morpholinyl, piperidinyl, piperazinyl or pyrrolidinyl, wherein the ring systems are optionally, including the nitrogen function, monosubstituted by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

or

R^6 and R^7 together with the nitrogen atom form a imidazolyl-, pyrryl-, morpholinyl-, piperidinyl-, pyrrolidinyl- or piperazinylring, wherein the ringsystems are optionally, including the nitrogen function, are monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, cyano or by a straight-chain or branched alkyl having up to 6 carbon atoms,

G represents phenyl, pyridyl, pyrimidyl, thienyl, furyl, pyrazolyl, isoxazolyl, thiazolyl, imidazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrrolidinyl or piperazinyl, wherein all above-mentioned residues and ring systems are optionally mono-substituted to trisubstituted by halogen, carboxyl, straight-chain or branched alkyl or alkoxycarbonyl each having up to 3 carbon atoms, pyridyl and/or by a residue of a formula $-NR^8-M-R^9$, $-NR^{10}-CO-NR^{11}R^{12}$, $-NR^{13}-SO_2-NR^{14}R^{15}$, $-SO_2-R^{16}$ or $-(SO_2)_a-NR^{17}R^{18}$,

wherein

a denotes a number 0 or 1,

M denotes a residue of formula SO_2 or CO

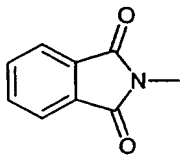
R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} and R^{18} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

R^9 denotes straight-chain or branched alkyl or alkoxy each having up to 3 carbon atoms,

R^{16} denotes benzyl, phenyl or methyl,

or

G represents straight-chain or branched alkyl or alkenylen having up to 4 carbon atoms, which are optionally monosubstituted to trisubstituted by halogen, phenyl, pyridyl, pyrimidyl, thienyl, furryl, imidazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl or by a residue of a formula $-NR^{19}R^{20}$ or



wherein

R^{19} and R^{20} have the abovementioned meaning of R^{11} and R^{12} and are identical or different to the latter,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula -CO-R^{21},

in which

R^{21} denotes straight chain or branched alkoxy having up to 3 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 3 carbon atoms,

R^4 represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl which are optionally up to trifold substituted by identical or different pyridyl, fluorine, chlorine, bromine, methoxy, trifluoromethyl, cyano, or by straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms

L represents an oxygen atom,

and salts thereof.

Very particularly preferred compounds of the general formula (I) are those,

in which

E and L represent an oxygen atom

and

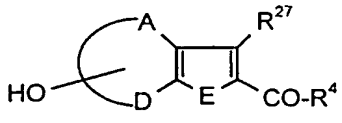
R^1, R^2 and R^3 represent hydrogen

and salts thereof.

A process for the preparation of the compounds of the general formula (I) has additionally been found, characterized in that,

that in the case in which R^5 denotes alkyl substituted by two vicinal hydroxyl-groups

[A] compounds of the general formula (II)



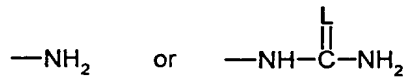
(II)

in which

R^4, A, D and E have the abovementioned meaning,

and

R^{27} denotes a residue of a formula



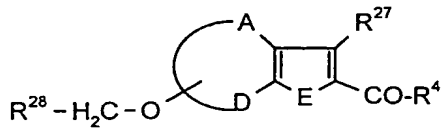
first are reacted with compounds of the general formula (III)

$$R^{28}\text{-}CH_2\text{-}Br \qquad (III)$$

in which

R^{28} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by phenyl or optionally nitro or halogen substituted phenyl and/or halogen,

in inert solvent and in presence of a base to compounds of the general formula (IV)



(IV)

in which

A, D, E, R^4, R^{27} and R^{28} have the abovementioned meaning,

and in a last step reacted with osmiumtetroxide (OsO_4) / N-methylmorpholino-N-oxide in inert solvents,

or

in the case in which R^5 denotes alkyl substituted by two to five hydroxyl groups

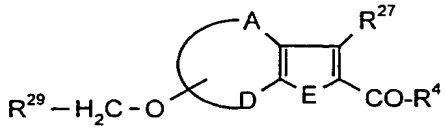
[B] compounds of the general formula (II) are reacted with compounds of the general formula (V)

$$R^{29}\text{-}CH_2OH \qquad (V)$$

in which

R^{29} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by hydroxyl,

in inert solvents and in the presence of triphenylphosphine / diethylazodicarboxylate to compounds of the general formula (VI)



(VI)

in which

A, D, E, R^4, R^{27} and R^{29} have the abovementioned meaning

and in a last step are reacted with OsO_4/N-methylmorpholino-N-oxide in inert solvents,

or

[C] compounds of the general formula (II) are reacted with alcohols of the general formula (VII)

$$R^5\text{-OH} \qquad \text{(VII)}$$

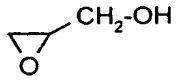
in which

R^5 has the abovementioned meaning

in inert solvents and in presence of triphenylphosphine / diethylazodicarboxylate

or

[D] compounds of the general formula (II) are reacted with the compound of the formula (VIII)



(VIII)

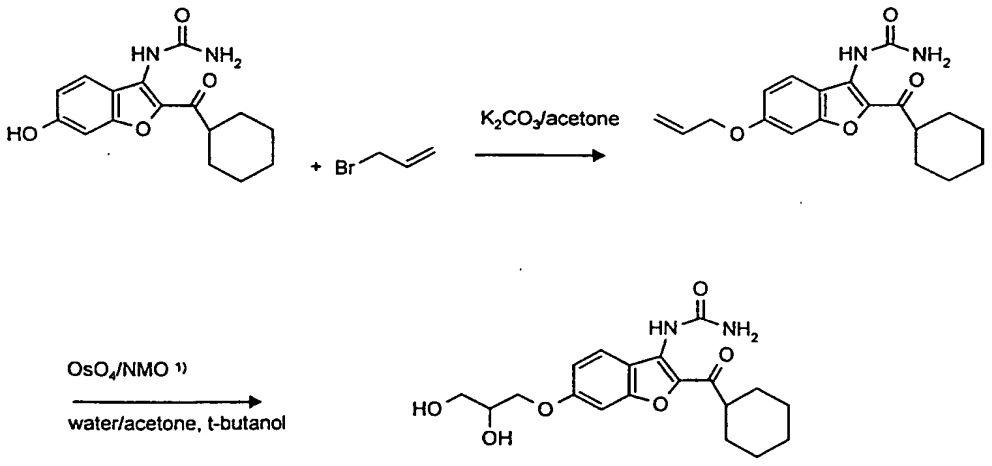
in inert solvents and in the presence of a base and titanium-(IV)isopropylate

and in the case

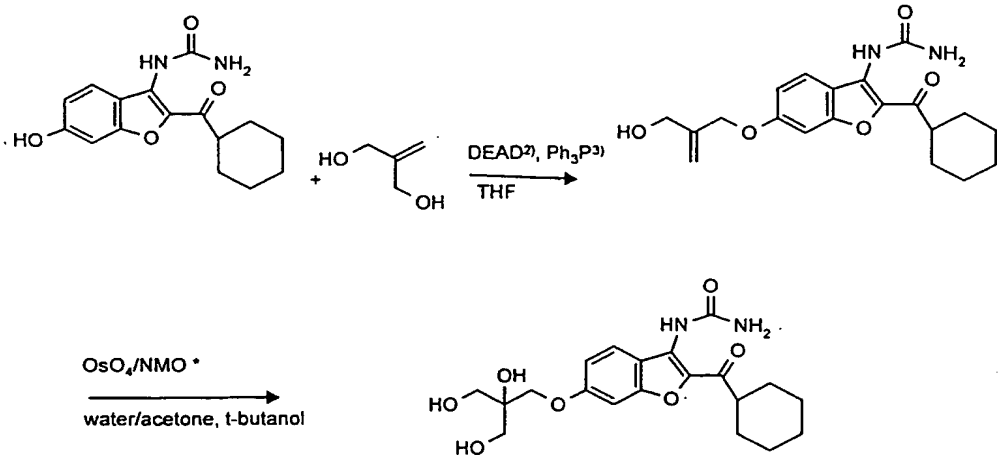
in which R^1, R^2 and/or $R^3 \neq H$ the amino groups are derivated optionally by common methods.

The process according to the invention can be illustrated by way of example by the following equations:

[A]

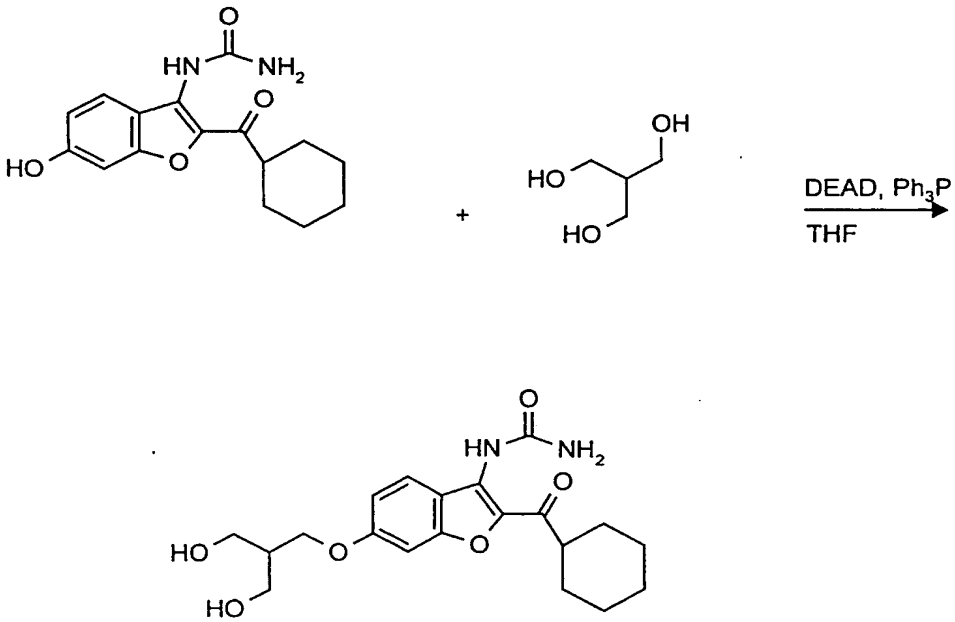


[B]

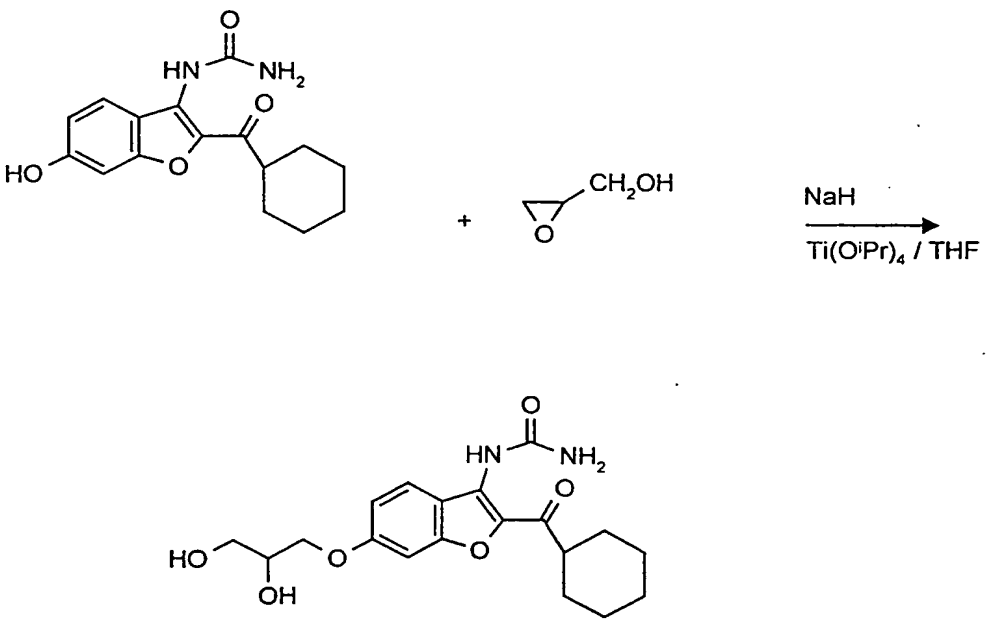


1) N-Methylmorpholino-N-oxide
2) diethylazodicarboxylate
3) triphenylphosphine

[C]



[D]



Suitable solvents for the different processes [A] - [D] are generally water or customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxan or tetrahydrofuran, ethylacetate, acetone, dimethylsulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol, butanol or t-butanol, or halogenohydrocarbons such as dichloromethane, dichloroethane, trichloromethane or tetrachloromethane. Acetone is preferred for the first step of [A] and water/acetone/t-butanol for all processes with OsO_4/N-methylmorpholino-N-oxide.

Tetrahydrofurane is preferred for the process with the systems triphenylphosphine / diethylazodicarboxylate

Suitable bases are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide, sodium hydrogencarbonate or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate,

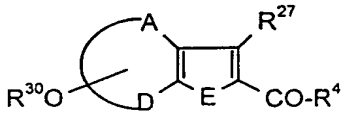
alkaline earth metal carbonates such as calcium carbonate, or organic amines (trialkyl-(C_1-C_6)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]-octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine or methyl-piperidine, or amides such as sodium amides, lithium butyl amide or butyllithium. It is also possible to employ alkali metals, such as sodium, or their hydrides such as sodium hydride, as bases. Sodium hydride for process [D] and potassium carbonate for the first step of [A] are preferred.

The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 4 mol, relative to 1 mol of the compounds of the general formula (II).

The processes are in general carried out in a temperature range from -30°C to +100°C, preferably from -10°C to +50°C.

The processes are generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (II) are known or new and can be prepared by reacting compounds of the general formula (IX)



(IX)

in which

A, D, E, R^4 and R^{27} have the abovementioned meaning

and

R^{30} denotes a hydroxyl protecting group, preferably methyl or benzyl,

by cleavage of the protecting group, wherein in the case of R^{27} = $-NH_2$ first compounds of the general formula (IX) are reacted with

compounds of the general formula (X)

$$R^{31}\text{-}N{=}C{=}L \quad (X)$$

in which

L has the abovementioned meaning

and

R^{31} has the above mentioned meaning of R^2 and R^3

in inert solvents, if appropriate in the presence of a base,

and in the case of R^2/R^3 = H and L = O,

compounds of the general formula (IX) are reacted with compounds of the general formula (XI)

$$X\text{-}SO_2\text{-}N{=}C{=}O \quad (XI)$$

in which

X denotes halogen, preferably chlorine,

and in the case von R^2/R^3 = H and L = S,

compounds of the general formula (IX) are reacted with NH_4SCN,

The hydroxyl-protective group is in case of R^{30} = benzyl in general removed with hydrogen in ethyl acetate, diethyl ether or tetrahydrofuran. Suitable catalysts are the noble metal catalysts, preferably palladium and palladium on charcoal .

Suitable solvents for the steps (IX/X and IX/XI) are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxan or tetrahydrofuran, ethylacetate, dimethylsulfoxide, dimethylformamide or halogenohydrocarbons such as dichloromethane, dichloroethane, trichloromethane or tetrachloromethane. Dichloromethane is preferred.

Suitable bases for these steps are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide, sodium hydrogencarbonate or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkaline metal or organic amines (trialkyl(C_1-C_6)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), pyridine or methylpiperidine or amides such as sodium amides, lithium butyl amide or butyllithium. It is also possible to employ alkali metals, such as sodium, or their hydrides, such as sodium hydride, as bases. Potassium carbonate, triethylamine, sodium hydrogencarbonate and sodium hydroxide are preferred.

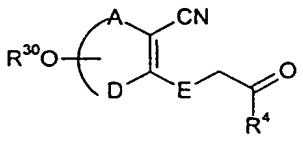
The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 4 mol, relative to 1 mol of the compounds of the general formula (IX).

The process is in general carried out in a temperature range from -30°C to +100°C, preferably from -10°C to +50°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (IX) are as species new and are prepared characterized in that,

first compounds of the general formula (XII)



(XII)

in which

A, D, E, R^4 and R^{30} have the abovementioned meaning,

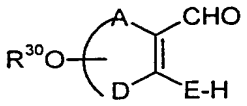
are reacted with a catalytic amount of alkali alcoholates such as sodium methanolate, sodium ethanolate or sodium propanolate. Sodium ethanolate ist preferred.

Suitable solvents for the the procedure are generally alcohols such as methanol, ethanol or propanol. Ethanol is preferred.

The process is in general carried out in a temperature range from 0°C to +60°C, preferably from room temperature to 60°C.

The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (XII) are as species new and can be prepared by reaction of compounds of the general formula (XIII)

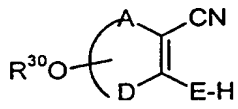


(XIII)

in which

A, D, E and R^{30} have the abovementioned meaning,

with hydroxylamine hydrochloride in a presence of sodiumformiate to compounds of the general formula (XIV)



(XIV)

in which

A, D, E and R^{30} have the abovementioned meaning,

and in a next step are reacted with compounds of the general formula (XV)

$$R^4\text{-CO-CH}_2\text{-T} \qquad \text{(XV)}$$

in which

R^4 has the abovementioned meaning,

and

T represents halogen. preferably bromine.

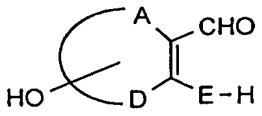
in inert solvents and in the presence of a base.

Suitable solvents are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxan or tetrahydrofurane, aceton, dimethylsulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol or halogenohydrocarbons such as dichlormethane, trichloromethane or tetrachloromethane. Acetone and dimethylformamide are preferred.

The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (IX) in which R^{27} denotes NH_2 can be prepared like described above or in a single step procedure by reacting compounds of the general formula (XIV) with compounds of the general formula (XV) in the presence of a surplus of sodium ethylate under reflux .

The compounds of the general formula (XIII) can be prepared by reaction of compounds of the general formula (XVI)



(XVI)

in which

A, D and E have the abovementioned meaning

with hydroxyl protecting agents of the general formula (XVII)

R^{30}-Z' (XVII)

in which

R^{30} has the abovementioned meaning

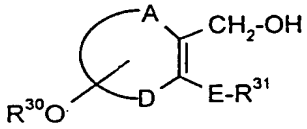
and

Z' denotes halogen, preferably chlorine or bromine

in inert solvents, preferably acetone or dimethylformamide,

and in the case of A and D = heterocycle,

by reaction of compound of the general formula (XVIII)



(XVIII)

in which

A, D, E and R^{30} have the abovementioned meaning,

and

R^{31} denotes methyl,

with MnO_2 followed by BCl_3 / CH_2Cl_2.

The compounds of the general formulae (III), (V), (VII), (VIII), (X), (XI), (XV) and (XVIII) are known and in some cases new and can be prepared by customary methods.

The compounds of the general formulae (II), (IV), (VI), (IX), (XII), (XIII), (XIV), (XVII) and (XVIII) are new and can be prepared like described above.

Surprisingly it was found that compounds given by the general formula (I) inhibited oxygen radical formation as well as TNFα (tumor necrosis factor) production. These compounds elevated cellular cyclic AMP by inhibition of phagocyte phosphodiesterase activity.

The compounds according to the invention specifically inhibit the production of superoxide by polymorphonuclear leukocytes (PMN). Furthermore, these compounds inhibit TNFα release in human monocytes in response to a variety of stimuli including bacterial lipopolysaccharide (LPS), complement-opsonized zymosan (ZymC3b) and IL-1ß. The described effects are probably mediated by the elevation of cellular cAMP due to inhibition of the type IV phosphodiesterase responsible for its degradation.

They can therefore be employed in medicaments for the treatment of acute and chronic inflammatory processes.

The compounds according to the invention are preferably suitable for the treatment and prevention of acute and chronic inflammation and auto immune diseases, such as emphysema, alveolitis, shock lung, all kind of COPD, ARDS, asthma and bronchitis, cystic fibrosis, eosinophilic granuloma, arteriosclerosis, arthrosis, inflammations of the gastro-intestinal tract, myocarditis, bone resorption diseases, reperfusion injury, Crohn's disease, ulcerative colitis, system lupus erythematosus, type I diabetes mellitus, psoriasis, anaphylactoid purpura nephritis, chronic glomerulonephtritis, inflammatory bowel disease, other benign and malignant proliferative skin diseases, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, sepsis and septic shock, toxic shock syndrome, grafts vs host reaction, allograft rejection,

treatment of cytokine mediated chronic tissue degeneration, rheumatoid arthritis, arthritis, rheumatoid spondylitis and osteoarthritis and coronary insufficiency, myalgias, multiple sclerosis, malaria, AIDS, cachexia, prevention of tumor growth and invasion of tissue, leukemia, depression, memory impairment and acute stroke. The compounds according to the invention are additionally suitable for reducing the damage to infarct tissue after reoxygenation. In this case the simultaneous administration of allopurinol to inhibit xanthine oxidase is of advantage. Combination therapy with superoxide dismutase is also of use.

Test description

1. Preparation of human PMN
Blood was taken from healthy subjects by venous puncture and neutrophils were purified by dextran sedimentation and resuspended in the buffered medium.

2. Inhibition of FMLP-stimulated production of superoxide racidal anions.
Neutrophils (2.5×10^5 ml^{-1}) were mixed with cytochrome C (1.2 mg/ml) in the wells of a microtitre plate. Compounds according to the invention were added in dimethyl sulphoxide (DMSO). Compound concentration ranged from 2.5 nM to 10 µM, the DMSO concentration was 0.1% v/v in all wells. After addition of cytochalasin b (5 µg x ml^{-1}) the plate was incubated for 5 min at 37°C. Neutrophils were then stimulated by addition of 4×10^{-8} M FMLP and superoxide generation measured as superoxide dismutase inhibitable reduction of cytochrome C by monitoring the OD_{550} in a Thermomax microtitre plate spectrophotometer. Initial rates were calculated using a Softmax kinetic calculation programme. Blank wells contained 200 units of superoxide dismutase.

The inhibition of superoxide production was calculated as follows:

$$\frac{[1-((Rx-Rb))]}{((Ro - Rb))} \cdot 100$$

Rx = Rate of the well containing the compound according to the invention.

Ro = Rate in the control well.

Rb = Rate in the superoxide dismutase containing blank well.

Compounds according to the invention have IC_{50} values in the range 0,07 μM-10 μM.

3. Measurement of PMN cyclic AMP concentration

The compounds according to the invention were incubated with 3.7 x 10^6 PMN for 5 min at 37°C before addition of 4 x 10^{-8} M FMLP. After 6 min protein was precipitated by the addition of 1% v/v conc. HCl in 96% v/v ethanol containing 0.1 mM EDTA. After centrifugation the ethanolic extracts were evaporated to dryness under N_2 and resuspended in 50 mM Tris/HCl pH 7.4 containing 4 mM EDTA. The cyclic AMP concentration in the extracts was determined using a cyclic AMP binding protein assay supplied by Amersham International plc. Cyclic AMP concentrations were expressed as percentage of vehicle containing control incubations.

Compounds elavate the cAMP-level at 1 μM compound 0-400% of control values.

4. Assay of PMN phosphodiesterase

This was performed as a particulate fraction from human PMN essentially as described by Souness and Scott (Biochem. J. 291, 389-395, 1993). Particulate fractions were treated with sodium vanadate / glutathione as described by the authors to express the descrete stereospecific site on the phosphodiesterase

enzyme. Compounds according to the invention had IC_{50} values ranging from 0,001 μM to 10 μM.

5. Assay of human platelet phosphodiesterase

This was performed essentially as described by Schmidt et al (Biochem. Pharmacol. 42, 153-162, 1991) except that the homogenate was treated with vanadate glutathione as above. Compounds according to the invention had IC_{50} values greater than 100 μM.

6. Assay of binding to the rolipram binding site in rat brain membranes

This was performed essentially as described by Schneider et al. (Eur. J. Pharmacol. 127, 105-115, 1986). Compounds according to the invention had IC_{50} values in the range 0,01 to 10 μM.

7. Preparation of human monocytes

Blood was taken from normal donors. Monocytes were isolated from peripheral blood by density centrifugation, followed by centrifugal elutriation.

8. Endotoxin induced TNF release

Monocytes (1×10^6 ml^{-1}) were stimulated with LPS (2 μg ml^{-1}) and coincubated with the compounds at different concentrations (10^{-4} to 10 μg ml^{-1}). Compounds were dissolved in DMSO/medium (2% v/v). The cells were incubated in RPMI-1640 medium glutamine/FCS supplemented and at 37°C in a humidified atmosphere with 5% CO_2. After 18 to 24 hours TNF was determined in the supernatants by an human TNF specific ELISA (medgenix). Controls were nonstimulated and LPS stimulated monocytes without compounds.

9. Endotoxin induced shock lethality in mice

B6D2F1 mice (n=10) were sensitized with galactosamine (600 mg/kg), and shock and lethality were triggered by LPS (0.01 μg/mouse). The compounds were administered intravenously 1 hour prior LPS. Controls were LPS

challenged mice without compound. Mice were dying 8 to 24 hours post LPS challenge.

The galactosamine / LPS mediated mortality was reduced.

10. Stimulation of human monocytes and determination of cytokine levels

Human monocytes ($2x10^5$ in 1 ml) were stimulated with 100 ng/ml LPS, 0.8 mg/ml zymC3b or 10 ng/ml IL-1ß in the presence of test compounds. The final DMSO concentration was maintained at 0.1 % v/v. Cells were incubated overnight in a humidified atmosphere of 5% CO_2 at 37°C. Supernatants were harvested and stored at -70°C. The TNFα concentration was measured by ELISA using the A6 anti-TNF monoclonal antibody (Miles) as the primary antibody. The secondary antibody was the polyclonal anti-TNFα antibody IP300 (Genzyme) and the detection antibody was a polyclonal anti-rabbit IgG alkaline phosphatase conjugate (Sigma). IL-10 was determined by ELISA (Biosource).

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, nontoxic, pharmaceutically suitable excipients or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration of about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent, organic solvents can be used as auxiliary solvents if appropriate.

Administration is carried out in a customary manner, preferably orally or parenterally, in particular perlingually or intravenously.

In the case of parenteral administration, solutions of the active compound can be employed using suitable liquid vehicles.

In general, it has proved advantageous on intravenous administration to administer amounts from about 0.001 to 10 mg/kg, preferably about 0.01 to 5 mg/kg of body weight to achieve effective results, and on oral administration the dosage is about 0.01 to 25 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

In spite of this, it may be necessary to depart from the amounts mentioned, in particular depending on the body weight or the type of application route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of administration of relatively large amounts, it is advisable to divide these into several individual doses over the course of the day.

Experimental Procedures

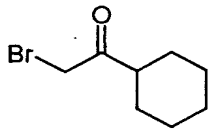
Thin Layer Chromatography Solvent Mixtures:

I	methylene chloride : methanol	100 : 2
II	methylene chloride : methanol	100 : 5
III	methylene chloride : methanol	10 : 1
IV	petroleum ether : ethyl acetate	3 : 1
IV	petroleum ether : ethyl acetate	1 : 1
V	methylene chloride	

Starting compound

Example I A

Bromomethyl cyclohexyl ketone



Prepared according to literature precedent (Gaudry, M.; Marquet, A. Tetrahedron 1970, 26, 5611): To a solution containing methyl cyclohexyl ketone (10 g, 79 mmol) in methanol (50 ml) at 0°C was added bromine (12 g, 79 mmol) dropwise over a period of 10 min. The resulting solution was allowed to stir at this temperature for 1 h and then water (25 ml) and ether (50 ml) was added. The two phases were separated and the aqueous phase extracted with ether (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4), concentrated and vacuum distilled (170°C, 17 mm Hg) to afford the title compound (11.8 g, 72%) as a yellow oil: NMR (300 MHz, $CDCl_3$) d 3.95 (s, 2H), 2,80-2.66 (m, 1H), 1.92-1.63 (m, 5H), 1.48-1.15 (m, 5H); MS (CI) 222 ($M + NH_4$).

The following examples were prepared in an analogous manner:

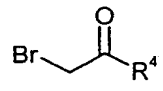


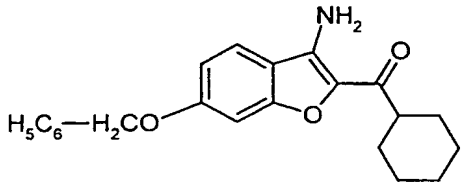
Table 1A

Couple No.	R^4	BP (°C / mm Hg)	Yield (% of theory)
2 A	c-C_3H_5	75 / 0.9	47 g (100)
3 A	c-C_4H_7	100 / 0.5	26 g (94)
4 A	c-C_5H_9	nd	4.4 g (95)
5 A	c-C_7H_{11}	150 / 1.0	3.9 g (51)

Preparation samples

Example 1

(3-Amino-6-benzyloxy-benzofuran-2-yl)-cyclohexyl-methanone



A suspension containing bromomethyl cyclohexyl ketone (8.37 g, 41 mmol), 5-benzyloxy-2-cyano-1-hydroxybenzene (7.48 g, 33 mmol) and caesium carbonate (21.9 g, 67 mmol) in DMF (80 ml) was heated to 60°C for 18 h. The resulting mixture was cooled to room temperature, concentrated to remove the DMF and partitioned between EtOAc (75 ml) and water (150 ml). The phases were separated and the aqueous phase extracted with EtOAc (2 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried (Na_2SO_4) and concentrated. The resulting residue was column chromatographed on silica gel (petroleum ether: EtOAc; 3:1) to afford the title compound (7.69 g, 66 %) as an off white solid: R_f 0.48 (IV), MP: 210°C.

The following examples were prepared in an analogous manner:

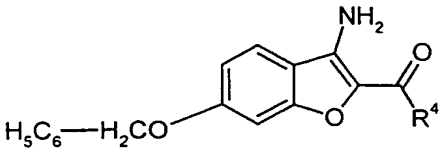
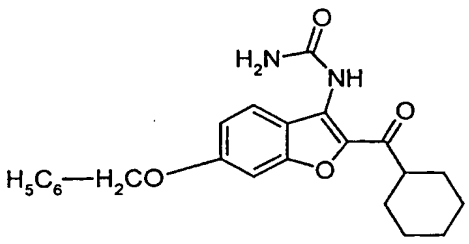


Table 1

Couple No.	R^4	MP (°C)	TLC	Yield (% of theory)
2	c-C_3H_5	156	0.31 (IV)	12 g (90)
3	c-C_4H_7	136	0.49 (I)	9.3 g (81)
4	c-C_5H_9	112	0.52 (I)	5.1 g (81)
5	c-C_7H_{11}	oil	0.33 (V)	3.7 g (77)

Example 6

(6-Benzyloxy-2-cyclohexanecarbonyl-benzofuran-3-yl)-urea



To a solution containing (3-amino-6-benzyloxy-benzofuran-2-yl)-cyclohexyl-methanone (8.25 g, 24 mmol) in CH_2Cl_2 (120 ml) at 0°C was added chlorosulfonyl-isocyanate (3.51 g, 25 mmol) dropwise over 30 min. The reaction mixture was maintained at this temperature for 4 h and then concentrated. Water (250 ml) was

added to the resulting residue and the mixture stirred for 18 h. The resulting suspention was filtered, the filter cake was washed with methanol and dried under vacuum to afford the title compound (6.83 g, 74%) as an off white solid: R_f 0.23 (I), MP: 210°C.

The following examples were prepared in an analogous manner (Table 2):

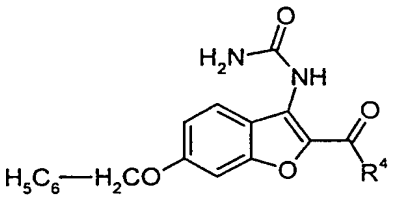
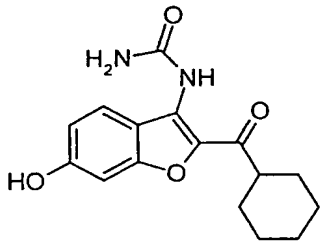


Table 2

Example No.	R^4	TLC	MP (°C)	Yield (% of theory)
7	c-C_3H_5	0.29 (II)	219	6.0 g (43)
8	c-C_4H_7	0.31 (I)	184	3.9 g (40)
9	c-C_5H_9	0.44 (II)	173	4.2 g (76)
10	c-C_7H_{11}	0.63 (II)	oil	1.9 g (25)

Examples 11

(2-cyclohexanecarbonyl-6-hydroxy-benzofuran-3-yl)-urea



To a suspension containing (6-benzyloxy-2-cyclohexanecarbonyl-benzofuran-3-yl)-urea (6.83 g, 17 mmol) in ethanol (700 ml), sodium formate (1.18 g, 17 mmol), formic acid (2.4 ml, 63 mmol) unter argon was added palladium on carbon (10%, 0.34 g). The resulting suspention was heated to reflux for 3 h and was then cooled to room temperature. The reaction mixture was filtered through celite and the filtrated concentrated. The resulting residue was purified by silica gel chromatography (CH_2Cl_2: ethanol; 100:5) to afford the title compound (4.58 g, 87%) as a pale yellow solid: R_f 0.10 (I), MP: 243°C.

The following examples were prepared in an analogous manner (Table 3):

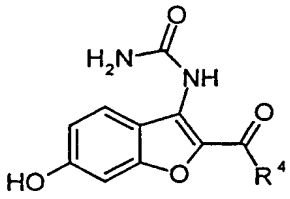
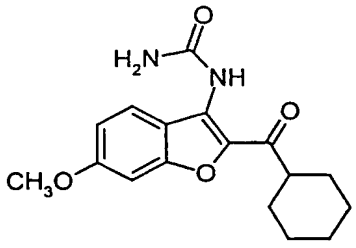


Table 3

Example No.	R^4	TLC	MP (°C)	Yield (% of theory)
12	c-C_3H_5	0.26 (II)	oil	1.8 g (68)
13	c-C_4H_7	0.25 (II)	oil	2.8 g (64)
14	c-C_5H_9	0.25 (II)	218	2.9 g (91)
15	c-C_7H_{11}	0.22 (II)	oil	3.0 g (100)

Examples 16

(2-cyclohexanecarbonyl-6-methoxy-benzofuran-3-yl)-urea



To a solution containing (2-cyclohexanecarbonyl-6-hydroxy-benzofuran-3-yl)-urea (500 mg, 1.6 mmol) in DMF (10 ml) and potassium carbonate (273 mg, 2.0 mmol) was added methyl iodide (281 mg, 2.0 mmol) and the resulting suspension was stirred at room temperature for 18 h. Water (20 ml) was added to the reaction mixture at which time a solid precipitated from solution. This solid was collected and washed with pentane to afford the title compound (520 mg, 99%) as a white solid: R_f 0.38 (II), mp: 227°C.

The following examples were prepared in an analogous manner (Table 4):

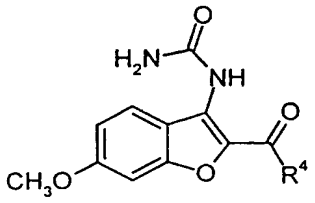
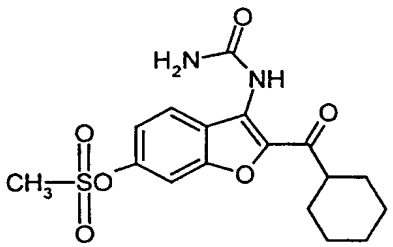


Table 4

Example No.	R^4	TLC	MP (°C)	Yield (% of theory)
17	c-C_3H_5	0.36 (II)	227	58 mg (36)
18	c-C_4H_7	0.46 (II)	218	250 mg (50)
19	c-C_5H_9	0.41 (II)	228	320 mg (61)
20	c-C_7H_{11}	0.52 (II)	203	60 mg (58)

Examples 21

Methanesulfonic acid 2-cyclohexanecarbonyl-3-ureido-benzofuran-6-yl ester



To a solution containing (2-cyclohexanecarbonyl-6-hydroxy-benzofuran-3-yl)-urea (250 mg, 0.83 mmol) and triethylamine (0.17 ml, 1.2 mmol) in DMF (15 ml) at 0°C was added methane sulfonylchloride (0.07 ml, 0.9 mmol) and the resulting suspention was stirred at this temperature for 2 h. The ice bath was then removed and the reaction mixture stirred for an additional 2 h. To reaction mixture was added water (10 ml) at which time a solid precipitated from solution. This solid was collected and washed with pentane and the resulting residue purified on a silica gel column (CH_2Cl_2: ethanol; 10:1) to afford the title compound (230 mg, 73%) as a white solid: R_f 0.47 (II), mp: 190 °C.

The following examples were prepared in an analogous manner (Table 5):

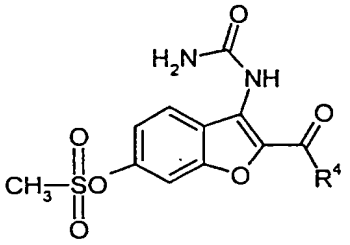
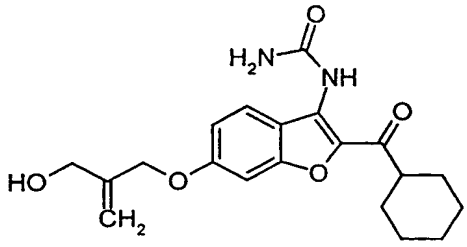


Table 5

Example No.	R^4	TLC	MP (°C)	Yield (% of theory)
22	c-C_3H_5	0.50 (II)	236	61 mg (48)
23	c-C_4H_7	0.51 (II)	204	406 mg (79)
24	c-C_5H_9	0.20 (II)	228	125 mg (20)
25	c-C_7H_{11}	0.49 (II)	212	107 mg (21)

Examples 26

[2-Cyclohexanecarbonyl-6-(2-hydroxymethyl-allyloxy)-benzofuran-3-yl]-urea



To a solution containing triphenylphosphine (2.12 , 8.1 mmol) in THF (40 ml) at 0°C was added diethyldiazodicarboxylate (1.3 ml, 8.1 mmol) and the resulting solution stirred at this temperature for 15 min. 2-Methylene-1,3-propanediol (0.72 g, 8.1 mmol) in THF (10 ml) was then added to the reaction mixture followed by (2-cyclohexanecarbonyl-6-hydroxy-benzofuran-3-yl)-urea (400 mg, 1.3 mmol) in THF

(10 ml). The resulting reaction mixture was maintained at 0°C for 30 min, the ice bath was then removed and the reaction stirred for an additional 18 h. The reaction mixture was then concentrated and the resulting residue purified on a silica gel column (CH_2Cl_2: ethanol; 100:5) to afford the title compound (355 mg, 72%) as a white solid: R_f 0.30 (II), mp: 175 °C.

The following examples were prepared in an analogous manner (Table 6):

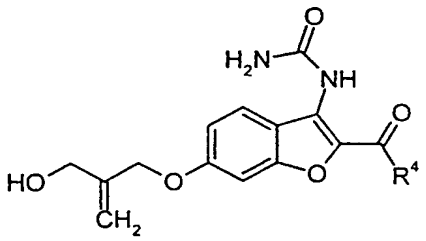
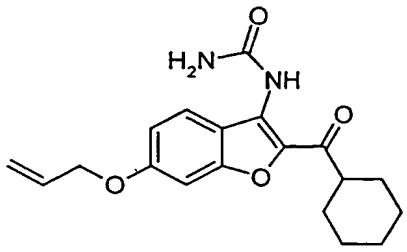


Table 6

Example No.	R^4	TLC	MP (°C)	Yield (% in theory)
27	c-C_3H_5	0.32 (II)	198	217 mg (52)
28	c-C_4H_7	0.30 (II)	171	257 mg (44)
29	c-C_5H_9	0.22 (V)	198	345 mg (56)
30	c-C_7H_{11}	0.33 (III)	205	107 mg (22)

Examples 31

(6-Allyloxy-2-cyclohexanecarbonyl-benzofuran-3-yl)-urea



To a solution containing (2-cyclohexanecarbonyl-6-hydroxy-benzofuran-3-yl)-urea (500 mg, 1.6 mmol) in DMF (10 ml) and potassium carbonate (285 mg, 2.1 mmol) was added allyl bromide (0.18 ml, 2.1 mmol) and the resulting suspention was stirred at room temperature for 18 h. Water (20 ml) was added to the reaction mixture at which time a solid precipitated from solution. This solid collected and washed with pentane to afford the title compound (366 mg, 65%) as a white solid: R_f 0.24 (II), mp: 178 °C.

The following examples were prepared in an analogous manner:

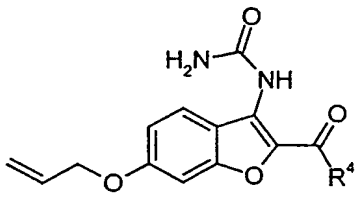
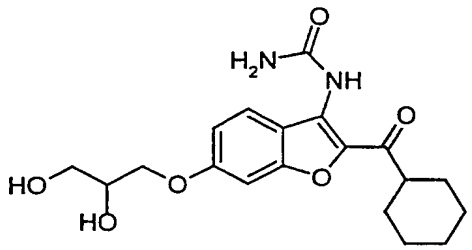


Table 7

Example No.	R^4	TLC	MP (°C)	Yield (% in theory)
32	c-C_3H_5	0.27 (II)	195	494 mg (71)
33	c-C_4H_7	0.38 (II)	190	390 mg (68)
34	c-C_5H_9	0.33 (II)	165	530 mg (92)
35	c-C_7H_{11}	0.38 (II)	170	618 mg (55)

Examples 36

2-Cyclohexanecarbonyl-6-(2,3-dihydroxy-propoxy)-benzofuran-3-yl]-urea



To a solution containing N-methylmorpholine-n-oxide (115 mg, 0.98 mmol) in water (7.5 ml) and acetone (15 ml) at room temperature was added osmium (IV) oxide (0.31 ml of a 2.5% solution in butanol) followed by (6-Allyloxy-2-cyclohexane-carbonyl-benzofuran-3-yl)-urea (316 mg, 0.92 mmol). The resulting reaction mixture was heated to 40°C and stirred at this temperature for 18 h. The resultion reaction mixture was cooled to room temperature and partitioned between ethyl acetate (25 ml) and water (25 ml). The phases were separated and the aqueous phase extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were dried (Na2SO4), concentrated and chromatographed on a silica gel column (CH_2Cl_2: ethanol; 10:1) to afford the title compound (238 mg, 67%) as a white solid: R_f 0.36 (III), mp: 232 °C.

The following examples were prepared in an analogous manner (Table 8):

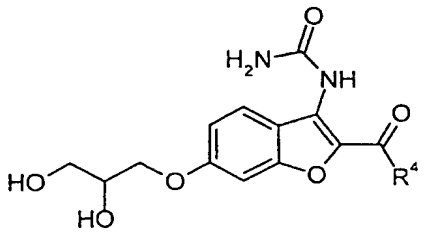
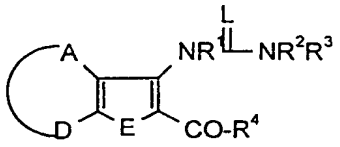


Table 8

Example No.	R^4	TLC	MP (°C)	Yield (% in theory)
37	c-C_3H_5	0.28 (III)	207	210 mg (44)
38	c-C_4H_7	0.42 (III)	170	260 mg (75)
39	c-C_5H_9	0.35 (III)	193	65 mg (30)
40	c-C_7H_{11}	0.36 (III)	195	88 mg (26)

We claim:

1. Cycloalkyl substituted 3-urea-benzofurane- and -pyridofurane-derivatives of the general formula (I)



(I)

in which

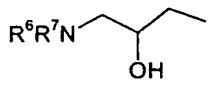
A and D including the double bond connecting them together form a phenyl-, pyridyl-, pyrimidyl, pyridazinyl- or thienyl-ring, which are substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having up to 10 carbon atoms, which is substituted difold to fivefold by hydroxyl or difold to fivefold by straight-chain oder branched alkoxy having up to 6 carbon atoms and wherein alkyl is optionally substituted by straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms, halogen, carboxyl or by phenyl, which is optionally substituted by nitro or halogen,

or

denotes a group of a formula



or $-SO_2-G$,

in which

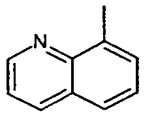
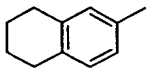
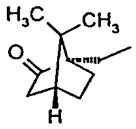
R^6 and R^7 denote hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by aryl having 6 to 10 carbon atoms or by a 5 to 7 membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused and which is optionally, including the nitrogenfunction, monosubstituted to disubstituted by identical or different substituents from the series comprising halogen, cyano or by straight-chain or branched alkyl, alkoxy or alkoxy-carbonyl each having up to 6 carbon atoms,

or

R^6 and R^7 together with the nitrogen atom form a 5- to 6-membered, aromatic, saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused and which is optionally, including the nitrogen-function, monosubstituted to disubstituted by identical or different substituents from the series comprising halogen, cyano or by straight-chain or branched alkyl or alkoxy-carbonyl each having up to 6 carbon atoms,

and

G denotes a residue of a formula



or


or aryl having 6 to 10 carbon atoms or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused, wherein all abovementioned residues and ring systems are optionally monosubstituted to trisubstituted by halogen, carboxyl, straight-chain or branched alkyl or alkoxycarbonyl each having up to 6 carbon atoms, pyridyl and/or by a residue of a formula $-NR^8-M-R^9$, $-NR^{10}-CO-NR^{11}R^{12}$, $-NR^{13}-SO_2-NR^{14}R^{15}$, $-SO_2-R^{16}$ or $-(SO_2)_a-NR^{17}R^{18}$,

wherein

a denotes a number 0 or 1,

M denotes a residue of formula SO_2 or CO

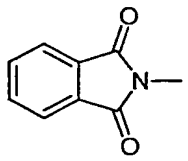
R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} and R^{18} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

R^9 denotes straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms.

R^{16} denotes benzyl, phenyl or methyl,

or

G denotes straight-chain or branched alkyl or alkenylen having up to 8 carbon atoms, which optionally are monosubstituted to trisubstituted by halogen, aryl having up 6 to 10 carbon atoms or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused or by a residue of a formula $-NR^{19}R^{20}$ or



wherein

R^{19} and R^{20} have the abovementioned meaning of R^{11} and R^{12} and are identical or different to the latter,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms, an amino protecting group or a group of the formula $-CO-R^{21}$

in which

R^{21} denotes straight chain or branched alkoxy having up to 4 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cycloalkyl having up to 6 carbon atoms, straight chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 8 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a 5- to 7-membered saturated heterocycle optionally having a further O atom,

R^4 represents cycloalkyl having up 3 to 8 carbon atoms which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, halogen, nitro, 1H-tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substuted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms or by a group of formula $-NR^{22}R^{23}$, $-SR^{24}$, $-(NH)_b-SO_2R^{25}$ or $-O-SO_2R^{26}$,

in which

R^{22} and R^{23} are identical or different and denote hydrogen or a straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^{22} denotes hydrogen

and

R^{23} denotes straight-chain or branched acyl having up to 6 carbon atoms

R^{24} denotes straight-chain or branched alkyl having up to 4 carbon atoms,

b denotes a number 0 or 1,

R^{25} and R^{26} are identical or different and represent straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, which are optionally substituted by trifluoromethyl, halogen or straight-chain or branched alkyl having up to 4 carbon atoms,

L represents an oxygen or sulfur atom

and salts thereof.

2. Compounds according to claim 1,

in which

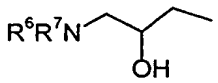
A and D, including the double bond connecting them form together a phenyl-, pyridyl- or pyridazinyl-ring, which are substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is substituted difold to fourfold by hydroxyl, and wherein alkyl is optionally substituted by straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms, fluorine, chlorine or by phenyl, which is optionally substituted by nitro, fluorine or chlorine,

or

denotes a group of a formula

 or $-SO_2-G$,

in which

R^6 and R^7 represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl, pyridyl, imidazolyl, pyrryl, morpholinyl, piperidinyl, piperazinyl or pyrrolidinyl, wherein the ring systems are optionally, including the nitrogen function, monosubstituted by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

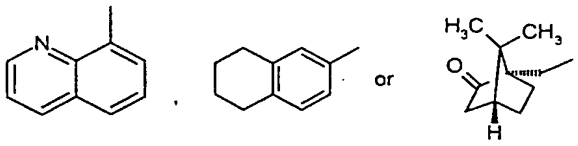
or

R^6 and R^7 together with the nitrogen atom form a pyrazolyl-, triazolyl-, tetrazolyl-, imidazolyl-, pyrryl-, morpholinyl-, piperidinyl-, pyrrolidinyl- or piperazinylring, wherein the

ringsystems are optionally, including the nitrogen function, are monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, cyano or by a straight-chain or branched alkyl having up to 6 carbon atoms,

and

G represents a residue of a formula



or phenyl, pyridyl, pyrimidyl, thienyl, furyl, pyrazolyl, isoxazol-yl, thiazolyl, imidazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrrolidinyl or piperazinyl, wherein all abovementioned residues and ring systems are optionally monosubstituted to trisubstituted by halogen, carboxyl, straight-chain or branched alkyl or alkoxycarbonyl each having up to 4 carbon atoms, pyridyl and/or by a residue of a formula $-NR^8-M-R^9$, $-NR^{10}-CO-NR^{11}R^{12}$, $-NR^{13}-SO_2-NR^{14}R^{15}$, $-SO_2-R^{16}$ or $-(SO_2)_a-NR^{17}R^{18}$,

wherein

a denotes a number 0 or 1,

M denotes a residue of formula SO_2 or CO

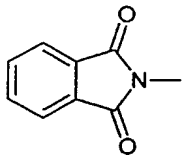
R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} and R^{18} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

R^9 denotes straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

R^{16} denotes benzyl, phenyl or methyl,

or

G represents straight-chain or branched alkyl or alkenylen having up to 6 carbon atoms, which are optionally monosubstituted to trisubstituted by halogen, phenyl, pyridyl, pyrimidyl, thienyl, furyl, imidazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl or by a residue of a formula $-NR^{19}R^{20}$ or



wherein

R^{19} and R^{20} have the abovementioned meaning of R^{11} and R^{12} and are identical or different to the latter,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms or a group of the formula -CO-R^{21}

in which

R^{21} denotes straight chain or branched alkoxy having up to 4 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 4 carbon atoms, or

or

R^2 and R^3 together with the nitrogen atom form a pyrrolidinyl-, piperidinyl- or morpholinyl-ring,

and

R^4 represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, fluorine, chlorine, bromine, nitro, tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having up to 4 carbon atoms, or by straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms

L represents an oxygen or sulfur atom.

3. Compounds according to claim 1 or 2,

in which

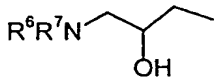
A and D, including the double bond connecting them form together a phenyl- or pyridyl-ring, which are substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is substituted difold to fourfold by hydroxyl, and wherein alkyl is optionally substituted by methoxycarbonyl, fluorine or by phenyl, which is optionally substituted by nitro or fluorine,

or

denotes a group of a formula



or $-SO_2-G$,

in which

R^6 and R^7 denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl, pyridyl, imidazolyl, pyrryl, morpholinyl, piperidinyl, piperazinyl or pyrrolidinyl, wherein the ring systems are optionally, including the

nitrogen function, monosubstituted by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

or

R^6 and R^7 together with the nitrogen atom form a imidazolyl-, pyrryl-, morpholinyl-, piperidinyl-, pyrrolidinyl- or piperazinylring, wherein the ringsystems are optionally, including the nitrogen function, are monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, cyano or by a straight-chain or branched alkyl having up to 6 carbon atoms,

G represents phenyl, pyridyl, pyrimidyl, thienyl, furyl, pyrazolyl, isoxazolyl, thiazolyl, imidazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrrolidinyl or piperazinyl, wherein all abovementioned residues and ring systems are optionally monosubstituted to trisubstituted by halogen, carboxyl, straight-chain or branched alkyl or alkoxycarbonyl each having up to 3 carbon atoms, pyridyl and/or by a residue of a formula $-NR^8-M-R^9$, $-NR^{10}-CO-NR^{11}R^{12}$, $-NR^{13}-SO_2-NR^{14}R^{15}$, $-SO_2-R^{16}$ or $-(SO_2)_a-NR^{17}R^{18}$,

wherein

a denotes a number 0 or 1,

M denotes a residue of formula SO_2 or CO

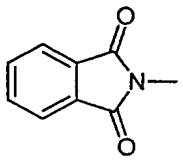
R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} and R^{18} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

R^9 denotes straight-chain or branched alkyl or alkoxy each having up to 3 carbon atoms,

R^{16} denotes benzyl, phenyl or methyl,

or

G represents straight-chain or branched alkyl or alkenylen having up to 4 carbon atoms, which are optionally monosubstituted to trisubstituted by halogen, phenyl, pyridyl, pyrimidyl, thienyl, furryl, imidazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl or by a residue of a formula $-NR^{19}R^{20}$ or



wherein

R^{19} and R^{20} have the abovementioned meaning of R^{11} and R^{12} and are identical or different to the latter,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula $-CO-R^{21}$,

in which

R^{21} denotes straight chain or branched alkoxy having up to 3 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 3 carbon atoms,

R^4 represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl which are optionally up to trifold substituted by identical or different pyridyl, fluorine, chlorine, bromine, methoxy, trifluoromethyl, cyano, or by straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms

L represents an oxygen atom,

and salts thereof.

4. Compounds according to any one of claims 1 to 3,

in which

E and L represent an oxygen atom

and

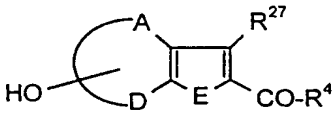
R^1, R^2 and R^3 represent hydrogen

and salts thereof.

5. A process for the preparation of the compounds according to any one of claims 1 to 4, characterized in that,

that in the case in which R^5 denotes alkyl substituted by two vicinal hydroxyl-groups

[A] compounds of the general formula (II)



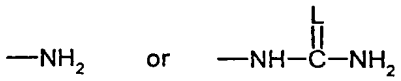
(II)

in which

R^4, A, D and E have the abovementioned meaning,

and

R^{27} denotes a residue of a formula



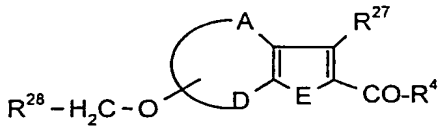
first are reacted with compounds of the general formula (III)

$$R^{28}\text{-}CH_2\text{-}Br \qquad (III)$$

in which

R^{28} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by phenyl or optionally nitro or halogen substituted phenyl and/or halogen,

in inert solvent and in presence of a base to compounds of the general formula (IV)



(IV)

in which

A, D, E, R^4, R^{27} and R^{28} have the abovementioned meaning,

and in a last step reacted with osmiumtetroxide (OsO_4) / N-methylmorpholino-N-oxide in inert solvents,

or

in the case in which R^5 denotes alkyl substituted by two to five hydroxyl groups

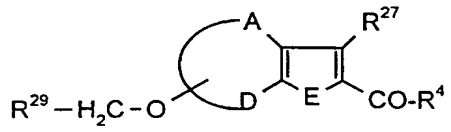
[B] compounds of the general formula (II) are reacted with compounds of the general formula (V)

$$R^{29}\text{-}CH_2OH \qquad (V)$$

in which

R^{29} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by hydroxyl.

in inert solvents and in the presence of triphenylphosphine / diethylazodicarboxylate to compounds of the general formula (VI)



(VI)

in which

A, D, E, R^4, R^{27} and R^{29} have the abovementioned meaning

and in a last step are reacted with OsO_4/N-methylmorpholino-N-oxide in inert solvents,

or

[C] compounds of the general formula (II) are reacted with alcohols of the general formula (VII)

$$R^5\text{-OH} \qquad \text{(VII)}$$

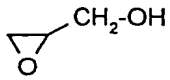
in which

R^5 has the abovementioned meaning

in inert solvents and in presence of triphenylphosphine / diethylazodicarboxylate

or

[D] compounds of the general formula (II) are reacted with the compound of the formula (VIII)



(VIII)

in inert solvents and in the presence of a base and titanium-(IV)isopropylate

and in the case
in which R^1, R^2 and/or $R^3 \neq H$ the amino groups are derivated optionally by common methods.

6. Compounds according to any one of claims 1 to 4 for therapeutic use.

7. The composition containing at least one compound according to any one of claims 1 to 4 and a pharmacologically acceptable diluent.

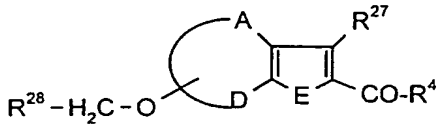
8. A composition according to claim 7 for the treatment and prevention of acute and chronic inflammatory processes.

9. The process for the preparation of compositions according to claim 7 and 8 characterized in that the cycloalkyl substituted 3-urea-benzofurane and pyridofurane derivative together with customary auxiliaries is brought into a suitable application form.

10. Use of compounds according to any one of claims 1 to 4 for the preparation of medicaments.

11. Use according to claim 10 for the preparation of medicaments for the treatment and prevention of acute and chronic inflammatory processes.

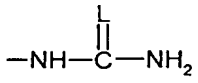
12. Compounds of the general formula (IV)



(IV)

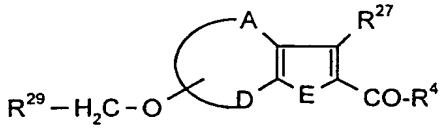
in which

A, D, E and R^4 have the abovementioned meaning,

R^{27} denotes a residue of a formula $-NH_2$ or 

R^{28} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by phenyl or optionally nitro or halogen substituted phenyl and/or halogen,

13. Compounds of the general formula (VI)



(VI)

in which

A, D, E, R^4 and R^{27} have the abovementioned meaning and

R^{29} denotes straight-chain or branched alkenyl haing up to 9 carbon atoms. which is optionally substituted by hydroxyl.

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(71) Applicant *(for all designated States except US)*: **BAYER AKTIENGESELLSCHAFT** [DE/DE]; D-51368 Leverkusen (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **STURTON, Graham** [GB/GB]; 184 Windsor Road, Maidenhead, Berkshire, SL6 2DW (GB). **FITZGERALD, Mary, F.** [GB/GB]; 2 Paternoster Court, Cassington Road, Yarnton, Oxford OXS 1QB (GB). **BRIGGS, Barbara, A.** [GB/GB]; 24 Latchmere Road, Kingston, Surrey KT2 5TN (GB). **CONCEPCION, Arnel** [PH/JP]; 3-6-207 Shibatsuji.cho, Nara City, Nara (JP). **BULLOCK, William** [US/US]; 60 Hermann Lane, Easton, CT 06612 (US). **BRÄUNLICH, Gabriele** [DE/DE]; Claudiusweg 9, D-42115 Wuppertal (DE). **ES-SAYED, Mazen** [DE/DE]; Ricarda-Huch-Str. 36, D-40764 Langenfeld (DE). **FISCHER, Rüdiger** [DE/DE]; Christian-Gau-Str. 33, D-50933 Köln (DE). **FUGMANN, Burkhard** [DE/DE]; Dr.-Kessel-Str. 3, D-40878 Ratingen (DE). **HENNING, Rolf** [DE/DE]; Am Jagdhaus 115, D-42113 Wuppertal (DE). **SCHNEIDER, Stephan** [DE/DE]; Am Ringofen 46, D-42327 Wuppertal (DE). **SPERZEL, Michael** [DE/DE]; Normannenstr. 31, D-42275 Wuppertal (DE). **SCHLEMMER, Karl-Heinz** [DE/DE]; Wildsteig 22a, D-42113 Wuppertal (DE).

(74) Common Representative: **BAYER AKTIENGESELLSCHAFT**; D-51368 Leverkusen (DE).

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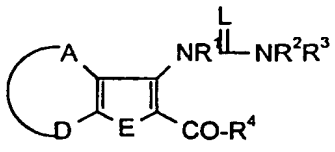
WO 00/69843 A3

(54) Title: CYCLOALKYL SUBSTITUTED 3-UREA-BENZOFURANE-AND -PYRIDOFURANE-DERIVATIVES



(I)

(57) Abstract: Cycloalkyl substituted 3-urea-benzofurane- and -pyridofurane-derivatives of general formula (I) for the treatment of inflammatory processes.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/EP 00/04012

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D307/82 A61K31/343 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 02440 A (BRAEUNLICH GABRIELE ;SCHNEIDER STEPHAN (DE); BAYER AG (DE); ESSAY) 22 January 1998 (1998-01-22) abstract; claims page 38 -page 51; examples; tables	1,6,7,9, 10,12,13
Y	EP 0 779 291 A (BAYER AG) 18 June 1997 (1997-06-18) abstract; claims 1,4	1,6,7,9, 10,12,13
Y	EP 0 146 243 A (MERCK FROSST CANADA INC) 26 June 1985 (1985-06-26) abstract; claim 1 page 141, line 10 - line 13 page 143, line 2 page 165; example 227 page 163; examples 197-201	1,6,7,9, 10,12,13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2000	14/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/EP 00/04012

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 731 099 A (BAYER AG) 11 September 1996 (1996-09-11) cited in the application page 48, line 42 - line 53; claim 1 page 36 -page 46; tables 3-6 abstract page 13; table I page 17; table I page 19 -page 21; tables II,III	1,6,7,9, 10,12,13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten nal Application No
PCT/EP 00/04012

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